We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

5

Oral Cancer and Potentially Cancerous Lesions – Early Detection and Diagnosis

C. S. Farah[1,2], P. J. Ford[1,2], K. Allen[1,2], A. Vu[1,2] and M. J. McCullough[3]
[1]*The University of Queensland, School of Dentistry, Brisbane*
[2]*The University of Queensland, UQ Centre for Clinical Research, Herston*
[3]*The University of Melbourne, Melbourne Dental School, Melbourne*
Australia

1. Introduction

Cancer of the oral cavity, also known as "oral cavity cancer" or more simply "oral cancer", affects the tongue, gingiva, floor of mouth, palate, tonsils and oropharynx.[1, 2] However, the most common form of oral cancer, oral squamous cell carcinoma (OSCC), can affect any tissue lined with oral mucosal epithelium.[2, 3] Oral cancer is one of the most common malignancies in the world, ranking eighth and thirteenth for males and females respectively.[1] Typically, patients with this cancer are over 40 years of age, although younger patients with regular exposure to risk factors associated with oral cancer can also present with potentially malignant and malignant oral mucosal lesions.[1, 3] Known aetiological risk factors include tobacco, betel quid, alcohol, and micronutrient deficiency.[1, 3, 4] Avoidance of these will reduce the probability of normal cells transforming to malignant cells.[4] In some cases though – namely, oral cancer in women under 45 years of age, tobacco use and alcohol consumption do not appear to play a role.[1] Instead, recent studies have suggested human papillomavirus (HPV) as a possible causative factor in cancers of the base of tongue, tonsils and oropharynx.[1, 2, 4]

Early detection of potentially malignant oral lesions (PMOLs) is important for improving the probability of complete recovery, since the stage of malignancy at the time of diagnosis influences morbidity and mortality.[1, 3, 5, 6] In most countries, the five-year survival rate is about 50% but can be as low as 15% if the cancer has spread to the lymphatic circulation.[1, 6] Unfortunately, more than 60% of patients present with stage III and IV oral cancer.[5] It is therefore important for all clinicians to recognize potentially malignant changes in oral mucosa and early-stage oral cancer in a visual and tactile examination, even though PMOLs may not become malignant.[1] In fact, only a small percentage of dysplastic lesions, and even fewer non-dysplastic lesions, undergo malignant transformation.[1, 3] PMOLs can be asymptomatic patches of white, red or speckled red-white,[1-3] with sharp or distinct borders and surface irregularity.[2] When these patches cannot clinically be characterised as any other condition, they are termed leukoplakia, erythroplakia and erythro-leukoplakia (speckled erythroplakia) respectively.[1] The most common PMOL is leukoplakia, although erythroplakia and erythro-leukoplakia have a higher likelihood of becoming malignant.[1-3] If undetected, they may turn into invasive cancer by growing or enlarging, causing tissue

destruction, induration, and fixation to deeper structures.[2, 3] Pain, dysesthesia, paraesthesia, loss of function, dysphagia, dysarthria, odynophagia, tooth mobility and cervical lymphadenopathy may also be present in invasive oral cancer.[2, 3] Hence, it is clearly important to detect potentially malignant oral mucosal lesions early.

Although many new technologies exist for helping clinicians detect lesions at an earlier stage, delay in detection still occurs, and this can be both patient and practitioner mediated, with patient delay contributing to the greatest proportion of total delay time. By targeting this delay, there is potential to detect lesions at an earlier stage, thus improving survival rates.

Screening programs serve to detect disease and allow for early intervention. In the case of oral cancer, early recognition and subsequent treatment of potentially malignant and malignant lesions is the key to improving 5 year survival rates.[7] Despite the fact that early detection and treatment increase survival rates and decrease morbidity, over the past few decades the 5-year survival rate has not significantly improved.[8] Despite the oral cavity being accessible to visual inspection, most cancers are diagnosed at a late stage of disease which can negatively impact prognosis.[9-12] Not only is survival compromised, but there is greater possibility for disfigurement and functional disturbances that can adversely affect the patient's quality of life post treatment.[13, 14] Diagnosis of oral cancer at an early asymptomatic stage is rare, with most patients seeking help only after the onset of symptoms.[9]

Delay in detection can be attributed to both the patient and practitioner and the key to improving survival rates is reduction of this delay. Patient delay is defined as the time between the patient's recognition of symptoms and their first consultation with a healthcare provider.[8] It is commonly recognized that patient delay constitutes the largest proportion of total delay time, although the amount varies between studies.[8, 10, 12, 15-20] Reasons for patient delay have been hypothesized and explored, however findings have been inconsistent. This may be in part due to differences in the population under study, study design or recall bias. Professional delay has been described as the time between a patient's initial consultation with a healthcare worker to the time of definitive diagnosis.[8] It has been proposed that only about 1 in every 63,000 patient visits will yield a positive tumour screen. This inherent rarity of detection may place the practitioner at a decreased vigil.[21] Although we rely partially on the patient to notice and present with symptoms, there is a professional and legal expectation on the dental practitioner to be able to identify a lesion and appropriately refer.[21] It is expected of general dental practitioners that upon patient presentation, oral cancer screening will occur.[22, 23]

Current literature has attempted to identify reasons for delay, however these appear to be diverse and dependent on the context of the study. Patient socioeconomic factors such as age or gender are usually not found to relate to duration of delay; neither are lesion factors such as size or location. Self medication has often been associated with longer delay. So while the knowledge base of this area of research is growing, more work is clearly needed. Further qualitative studies are required to explore factors which influence both patient and practitioner behaviors surrounding oral cancer detection and diagnosis. Qualitative methods are capable of eliciting contextually rich information to provide greater insights into factors associated with delay. Screening for oral lesions is not occurring consistently, with practitioners often citing a lack of time, financial incentives or training as barriers. Dental and medical practitioners are often unaware of where their duty lies in terms of

screening for oral cancer, however both disciplines express the need for education on both oral cancer detection and referral pathways. Further research is required in this field to inform effective interventions.

2. Screening

Oral cancer screening is 'the process by which a practitioner evaluates an asymptomatic patient to determine if he or she is likely or unlikely to have a potentially-malignant or malignant lesion'.[2] This definition implies more than a visual and tactile examination of the oral mucosa and includes assessment of the patient's risk profile - at a minimum a consideration of their age, tobacco and alcohol use. The aim of screening is to enhance the early detection of oral cancer and pre-cancer, and thereby enhance patient survival and outcomes. Due to the relatively low prevalence of oral cancer, population based screening is not currently justified.[24] Opportunistic screening (conducting an oral mucosal examination when the patient presents for periodic examination or other treatment), or targeting of groups known to be at higher risk for oral cancer is likely to be more cost-effective.[25] The profile of a high risk individual is that of an older male with a heavy use of tobacco and alcohol, poor diet and of low socioeconomic status.[9, 26] Emerging knowledge of the role of human papillomavirus (HPV) in the pathogenesis of oral cancer however is challenging the relevance of this profile. HPV positive oral cancer is associated with younger age and does not appear to be linked with gender, alcohol or tobacco use.[27, 28]

While the purpose of screening is to detect oral lesions, it also provides an excellent opportunity for the practitioner to engage the patient in a discussion about oral cancer. This serves to raise patient awareness about oral cancer generally, its risk factors and the importance of the screening examination that has just been performed. Patients may also examine themselves for early signs of oral cancer, however evidence for the usefulness of this approach is currently limited.[29, 30] The effectiveness of any screening program will be influenced by a number of factors. These factors include those relating to the patient, the practitioner, the availability and demonstrated efficacy of diagnostic aids, and those factors relating to the health system. These will be discussed in detail in the following sections.

3. Patient factors

Patient delay is defined as the time it takes for patients to seek help following self discovery of symptoms.[8] This term is widely accepted however it should be interpreted cautiously so as not to infer blame on the part of the patient. The mean patient delay varies between studies, with anywhere from 11 weeks to 6 months cited.[12, 17] Mean patient delay can be affected by large outliers in studies and for this reason it is useful to also include median delay, however not all studies report both.[31] Some studies collect data on a categorical basis, reporting the percentage of patients that present within a given time frame. It is difficult to define what excessive patient delay is, however a reduction in mean and median values would improve survival rates.

3.1 Public awareness of oral cancer

The public know little about the clinical presentation of oral cancer, although most are aware it is usually detected in late stages of disease.[32] Most people are able to identify

tobacco and previous experience of oral cancer as risk factors, but less people are aware of other risk factors such as alcohol, older age and poor diet.[32] Flyers and brochures in dental clinics may increase awareness of oral cancer. They may not only prompt patients to request a mucosal screening, but also motivate them to be more aware of self screening opportunities.[33] Leaflets have been shown to render patients more open to mucosal screening, with educational self screening pamphlets also resulting in high compliance.[33, 34] Not all practices however will promote awareness of oral cancer, as they believe it will create patient anxiety.[6, 35] This worry was unfounded in a study of dental professionals who attempted to integrate screening into their practices, finding patients had a positive disposition towards screening for oral cancer.[35] Although most patients were aware of oral cancer, some reported being totally unaware of the potential for it to occur.[16] Most patients who were aware of oral cancer had minimal knowledge.[16] Lack of awareness and knowledge of oral cancer has been reported to increase patient delay, thus making information available to patients may be a vital part in improving survival rates.[21] Although surgeries can make pamphlets available in the waiting room, it has been shown in numerous studies that those patients most at risk of developing oral cancer do not regularly attend a dentist.[21, 36-38] Television has the potential to reach a wider audience and educate about the importance of self screening and prompt presentation to a practitioner. Following an oral cancer campaign in Scotland, two thirds of those surveyed remembered hearing about oral cancer six months prior.[39] The majority of those patients saw it on television.[39] Around half of the patients felt encouraged to seek help because of the campaign.[39] In another study, several patients diagnosed with oral cancer remember having seen a television commercial, with two patients presenting to a health care professional as a result of these commercials.[16] Although television has the potential to reach a wide audience, oral cancer has a relatively low prevalence. For this reason it has been suggested a more cost effective mechanism is to target those most at risk of the condition.[40]

3.2 Self medication contributing to delay

Scott *et al.* performed a systematic literature review of articles published between 1975 and 2005 to identify known factors associated with patient delay.[20] The majority of factors investigated in studies reviewed were not shown to be related to the duration of patient delay. This may be because studies regarding patient delay are few in number and not all are considered rigorous in terms of study design.[20] In Thailand, it was reported that patients who had used traditional herbal medicine had a longer duration of delay.[20, 41] Self medication being associated with longer duration of patient delay has since been demonstrated in other studies. Patients may attempt to treat symptoms with over the counter products, with some seeking advice from pharmacists who commonly advise gels, creams or mouthrinses.[16, 42] These patients then wait to see whether their oral condition resolves following self medication, increasing duration of delay.[18] This highlights the importance of the pharmacist's awareness of oral cancer as they may be an initial point of call for a patient developing oral symptoms.[37, 42] One study showed that after pharmacies were given an educational package on oral cancer, more staff advised a mystery shopper querying a 4 week old non healing ulcer to present to a healthcare practitioner.[43] Although the shopper could be advised to visit either their doctor or dentist, most staff advised the shopper to visit a doctor.[43] Following the intervention only 45% of staff advised help seeking behavior, however this was higher than prior to the intervention.[43] A limitation of this study

was that only one staff member was approached at each pharmacy, and this may not have been representative of the overall impact of the educational material provided. Not only are patients self medicating symptoms before diagnosis, one study has demonstrated that patients often trial alternative therapies before undergoing conventional cancer treatment.[44]

3.3 Socio demographic factors contributing to delay

Studies consistently report no correlation between age and delay, however, whether other factors such as gender, financial status, location or size of lesion play a role in patient delay has not yet been substantiated, with studies often generating conflicting results.[8, 15-17, 41, 45-50] Gender is not usually demonstrated to influence duration of delay[8, 15-17, 41, 47-49, 51]. Only one study contradicted this, with women taking longer to present to a practitioner following self discovery of symptoms.[12] However in this study there was a male/female ratio of 5.4/1, with only a small number of females.[12] Two studies noted unmarried patients exhibit longer delay, both suggesting this is because married patients have more support.[17, 52] As other studies did not show marital status influenced delay, the differences may be a result of cultural factors. Two studies found longer delay in non smokers.[17, 45] Patients who do not smoke may feel that since they are at lesser risk of developing oral cancer, their lesion is not of concern.[17] This being said, patients who smoke and drink alcohol are more likely to present with concurrent illness and they often have poorer prognosis partly due to increased delay.[53] Heavy drinkers have been shown to display an increased duration of delay, and in the same study only light smokers demonstrated excessive delay.[54] Difficulty obtaining access to a practitioner is often shown to influence delay.[19, 55] A study comparing the waiting time for patients to see a dentist established that those with potentially malignant lesions (ulceration) were seen much faster than those requesting prosthetic treatment, showing dental surgeries will prioritise cases.[56] Eleven percent of appointments in this study were made because of symptoms similar to oral cancer. Unfortunately however a comparison of waiting times for other symptoms such as prolonged pain or numbness was not incorporated.[57] Patients afflicted with oral cancer are often of low socioeconomic background and financial barriers may play an important role in patient delay.[55] Practitioners agreed that patients of low socioeconomic background exhibited greater delay.[58] This is exemplified by the high patient delay experienced in the USA compared to Canada.[10] The USA has a healthcare system whereby individuals pay for their own health expenses, whereas in Canada some healthcare is provided by the government. One study did however report that most individuals in the USA diagnosed with oral cancer had health insurance coverage, and those that had no coverage did not exhibit excessive delay.[46] A study performed in the UK reported that an oral cancer patient waited to see a free NHS dentist rather than be seen immediately by a private dentist, for which a fee would be charged.[8] Only three out of 44 patients interviewed in England identified costs of a dental check up to be a large barrier.[42] Financial barriers are dependent on the health care system utilised in the country where the research is performed, further complicating study comparisons.

3.4 Lesion factors contributing to delay

Most studies have found tumour factors such as site, symptoms, size and stage did not have an association with duration of delay.[8, 18, 41, 47] One study indicated that patients with oral cancer located in more commonly found sites such as the tongue, floor of mouth and retromolar pads presented faster than those with cancer located in uncommon sites such as on the hard palate and gingivae.[12] However the small number of individuals with cancer in

uncommon sites in this study means that the results should be interpreted with caution.[12] Another study also showed that lesion site was associated with delay, but again a small sample size of uncommon cancer sites meant they were also unable to draw strong conclusions.[15] Those with cancer in more visible sites such as the lip or tongue have been shown to be diagnosed at earlier stages than others.[49] A lesion's maximal diameter was shown to be inversely proportional to delay by one study.[15] The patient's interpretation of symptoms has commonly been shown to influence duration of delay. The most common oral symptoms noticed by a patient are a non healing ulcer or sore, persistent lumps or swellings, sore tongue or mouth and sore throat, abscess or boil.[42, 49] Patients sometimes attribute these symptoms to an infection, dental problem or problem with a prosthesis.[51] Those that believe their lesion to be innocuous will often wait longer to be seen by a health care practitioner.[8, 18, 42, 51, 59] Some patients are aware there is a chance their symptoms are cancerous, but do not believe they are.[59] This highlights the need for both awareness of oral cancer presentation and the understanding that anyone may be afflicted. One study revealed patients also require guidance on how to interpret oral symptoms.[40] Of patients diagnosed with oral cancer, most can retrospectively pinpoint symptoms attributable to cancer and the majority of patients diagnosed with oral cancer report presenting as a result of their symptoms.[16, 46] This being said, symptom recognition is not a reliable method of detecting tumours at an early stage since about 25% of oral cancers remain silent until they reach an advanced size.[21] Although tumours may not necessarily be detected at an early stage, attribution of symptoms to cancer can at least lead to earlier detection.

3.5 Barriers and triggers to help seeking

Understanding the barriers and triggers to help seeking is crucial to institute effective mechanisms to decrease patient delay. Patient delay should not be influenced by whether the patient actually has a malignant lesion, since both benign and malignant lesions can exhibit similar symptoms. Despite this, most studies only include patients with a diagnosis of oral cancer. A more recent study took this into account and included patients who had potentially malignant lesions.[19] As was the case with patients diagnosed with oral cancer, patients delayed seeking help as they believed their symptoms were minor and some attempted self care prior to seeking help.[19] One study hypothesized that patients who had previously experienced benign lesions may have longer delay time, since they are less inclined to believe their condition needs attention.[15] Some patients had a negative attitude towards dental practitioners due to a previous negative experience or apprehension, with others not wanting to waste practitioners' time.[19, 51] Only about half of the patients interviewed in the USA had a regular dentist.[46] Often patients were found to have competing responsibilities or priorities such as work commitments or comorbidities.[19] Most previous studies have only looked at the barriers to help seeking. In order to institute effective public awareness however, triggers should also be identified. One study which queried patients about the triggers, found patients presented following either a change in symptoms, if they had another reason to visit a practitioner, had a fear of worsening symptoms, excessive worry, dislike of symptoms or were advised by significant others.[19] Attribution of symptoms to something sinister will not always inspire help seeking behaviour, with a fear of diagnosis sometimes leading to delay.[55] Another study also investigated triggers to presentation, finding the dominant triggers to be anxiety and worry, need to resolve uncertainty, avoidance of problems getting worse and being advised by others to seek help.[42] Being advised by others to seek help has been shown to trigger help

seeking behavior in subsequent studies, as well as receipt of new information from sources such as media or medical literature.[59] Development of a neck mass usually inspires a patient to visit a healthcare practitioner, however by this stage it is well advanced.[51] Most studies are conducted retrospectively, meaning they are subject to significant recall bias. Gao *et al.* instituted a system whereby family members were requested to confirm descriptions in order to decrease recall bias.[15] It was however found by Rogers *et al.* that the majority of patients will wait up to a month before telling anyone about their symptoms.[42] It is not apparent whether family members will be subject to the same recall bias, or simply tend to agree with the patient.

4. Practitioner factors

As with patient delay, a wide variance of mean and median professional delay time has been cited. This can be attributed to differing definitions of delay, recall bias or incomplete records. Although professional delay does not tend to contribute greatly to total delay, it is arguably the easiest part of delay to target. Professional delay has been proposed to occur as a result of lack of rigour in screening, lack of confidence in detection, low prevalence rates, inadequate knowledge and lack of incentives for screening.

4.1 Mucosal examination

A dentist's attitude to screening is an important factor in detecting early malignancy, as unless patients present with a complaint there is complete reliance on the dentist to identify mucosal lesions.[60, 61] It has been shown that patients who develop an oral cancer and who regularly attend a dentist are more likely to have their cancer diagnosed in its early stages.[46] Often, asymptomatic lesions are discovered incidentally during dental examination.[47, 62, 63] However, even following a routine dental examination malignant lesions are sometimes missed. This was demonstrated in a study where oral and maxillofacial surgeons detected oral cancer in patients referred for extraction of teeth.[47] The majority of dentists claim to perform mucosal screening for every patient, and in some cases they target screening to individuals over the age of 40.[14, 64] Of dentists working in nursing homes in Ohio, 83% reported performing mucosal exams for each patient, although only half actually identified increasing age as a risk factor for oral cancer.[65] Screening practices are found to be inconsistent between studies; only a third of dentists in Germany reported performing routine oral cancer examinations.[66] In the same study, only 66% of dentists questioned felt adequately trained to examine patients for oral cancer, despite the majority agreeing that dentists are qualified to perform these examinations.[66] In this study, questionnaires were sent out with a dental association journal and there was a response rate of only 14%, resulting in biased data, so the real picture is likely to be even worse.[66] Similar results were found in a separate study when questionnaires were sent to dental and medical professionals.[67] Although some practitioners cited a lack of time as a barrier to screening, the reality is that it takes less than 2 minutes to perform a thorough head and neck exam.[35, 38] Lack of financial incentives to perform mucosal screening may therefore be impeding on motivation to do so.[35] Almost all dentists surveyed in a study in Ohio felt oral cancer screening should be a separate reimbursable procedure, with all agreeing mucosal examinations should occur for all patients over 40 annually.[65] Lack of rigour regarding screening may be the result of the relatively low incidence of oral cancer; the average dentist

only encounters about 2 tumour cases during a lifetime.[21, 61] Clinicians should however be performing mucosal examinations not only to pick up cancer, but also other lesions, including potentially malignant lesions. What motivates a clinician to undertake a mucosal exam is yet to be determined, however if practitioners are only undertaking a mucosal exam to detect oral cancer the low prevalence rates may indeed play a role.

4.2 Risk assessment

Alcohol and smoking are prominent risk factors for of oral cancer.[7] Some practitioners will take this into account and perform a more thorough mucosal exam for smokers while others do not consider this a factor influencing their screening behaviour.[61, 68] One study demonstrated that dentists will often take into account risk factors when deciding whether to refer.[22] Dentists are in a position to provide smoking cessation advice. It has been shown however that some dentists don't believe there is any benefit providing this advice due to lack of financial incentives, a belief that people do not want the advice or the belief that patients do not want to quit.[6, 37, 69] The belief that patients don't want smoking cessation advice has been contradicted since, with about half the dental patients surveyed suggesting they would try to quit if advice was offered.[69] Almost two thirds of dentists questioned in Germany agreed dentists should be trained to provide smoking cessation, but only about a quarter felt they were able to provide advice.[66] Although a number of dentists claimed to provide smoking cessation advice, only a small number follow up with the patient and help them to quit.[64] The number of dentists requesting information about and providing advice on a patient's drinking habits has consistently been even lower.[37, 64, 66] This may be a result of less awareness of the role of alcohol in oral cancer.[37] About two thirds of dentists surveyed in Germany believed dentists should be trained to provide smoking cessation advice, and more than 50% felt training in alcohol cessation was important.[66] It has been suggested that compulsory continuing education should be implemented to educate practitioners about the effects of tobacco and alcohol on the oral mucosa and how to provide cessation advice.[64] Although practitioners may be aware of the risk that alcohol and smoking pose to the patient, there is still a lack of readiness to provide support to patients in modifying their risk behaviors. Patients diagnosed with oral cancer don't always link their smoking habits as a causative factor, highlighting the importance of public awareness of risk factors.[16] Targeting high risk groups for screening has been proposed as a feasible screening plan.[21] Practitioners involved could be trained to assist patients with reducing their risk from lifestyle factors such as tobacco and alcohol. They would therefore not only detect lesions earlier but also work with their patients to help them reduce their risk. Diagnostic delay has been associated with increased co-morbidities, which is concerning as over 25% of head and neck cancer patients also have illness in more than one body part.[53] These co-morbidities are often tobacco associated.[53]

4.3 Practitioner knowledge of oral cancer

It has been shown in some studies that practitioners lacked confidence in detecting cancer; however this has been contradicted in other studies.[14, 61] Dentists are often looking for cancer as opposed to potentially malignant lesions. Changing this philosophy is important in ensuring lesions are identified at an early stage where treatment is less radical.[61] Dentists should be able to determine whether a lesion has malignant potential or is already malignant, with non homogenous lesions being referred straight away.[7] Non homogenous

leukoplakia is often shown to have a marked increase in malignant change when compared with homogeneous leukoplakia.[7, 70] Erythroplakia exhibits higher malignant potential, with about half these lesions showing invasive carcinoma.[7] Alarmingly, health care providers surveyed in Scotland were more concerned about leukoplakia than erythroplakia.[37] This study included general medical practitioners as well as general dental practitioners with no distinction between groups in terms of oral cancer knowledge. Another study suggested that dentists do give due concern to erythroplakia.[61] A study comparing oral cancer knowledge between doctors and dentists found that dentists could identify more risk factors and oral changes associated with oral cancer.[68] It was shown that dentists are more confident in detecting oral cancer than doctors, despite most patients presenting to their doctor regarding oral lesions.[11, 21, 37, 42, 47] Patients may present to a doctor rather than a dentist because they do not view their oral lesion as a problem with their dentition or dentures, thus there is a need for the public to be made aware that it is appropriate to go to their dentist if they become aware of a mucosal lesion.[47] Doctors perceive lack of training and time to be barriers to oral cancer screening, similar to the dentist's disposition.[37] Doctors could be advised that if there is an oral condition they are unsure of, patients can be advised to seek the opinion of a dentist. It could be argued that this referral could contribute to delay, however Macpherson *et al*. found most doctors will refer if a lesion persists for 4-5 weeks compared to most dentists who wait only the recommended 2 weeks.[37] Although Jovanovic *et al*. found no significant difference in delay between doctors and dentists, their study analysed the records of 41 patients whereas Macpherson *et al.* sent questionnaires to 357 doctors and 331 dentists.[37, 47] Using questionnaires to record behavior introduces bias in itself, making interpretation difficult.

4.4 Need for continuing education

When practitioners are interviewed, they often exhibit the belief that there should be compulsory continuing education courses in oral cancer.[35, 58] Participants in one study wanted to know more about referral pathways, biopsy procedure and guidelines for screening.[35] Courses have been shown to be effective in promoting screening methods, with practitioners reporting better screening habits following attendance.[35, 58] A lack of confidence in detection has been made apparent as some dentists did not feel that they should deal with diseases such as cancer as they are "not medical doctors".[35] This lack of confidence also extends to doctors, as both doctors and dentists felt that they had inadequate training and were not confident in detecting oral lesions.[37] If that is the case, further compulsory continuing education courses on oral cancer could help to shift this belief and make practitioners more aware of their responsibility. Practitioners who have undertaken more recent continuing education courses in oral cancer have had greater knowledge in the area.[14] Despite the benefit of such courses, about one third of dentists from a Western US multistate dental practice group reported having never attended a continuing education course on oral cancer.[14] An association has been demonstrated between knowledge of risk factors and diagnosis, and number of lesions referred or biopsied by a practitioner.[71]

4.5 Referral and patient mediated professional delay

Some studies have found dentists will wait 2 weeks to review a lesion prior to referral. This is recommended since oral cancer can mimic traumatic lesions which resolve in 2 weeks.[6, 37,

[50] A difficulty in implementing the two week rule is that patients may delay in presentation for the second appointment, for reasons similar to initial delay.[72] In some cases, patients can also delay in effecting a referral.[58, 72] For this reason practitioners should convey urgency to the patient if a suspicious lesion is referred.[50] Not only should practitioners convey urgency to the patient, but also to the specialist, since mentioning malignancy or possibility of a tumour in the referral letter, or accompanying a referral letter with a phone call can categorise a referral as urgent.[50] Specialists will prioritise a patient if malignancy is suspected. Dentists have been shown to display difficulty in conveying their suspicions in referral letters, especially when compared to their medical counterparts.[73] Practitioners should also follow up referred patients to ensure they are utilising their referral, effectively decreasing this proportion of professional delay.[72] Patient anxiety has been shown to modify the decision to refer.[6, 61] Although it is important to allay the concerns of an anxious patient, a suspicious lesion should be referred regardless of whether the patient is concerned. Cues for frank malignancy are more likely to prompt a referral when compared with premalignancy and it has been demonstrated in numerous studies that if a practitioner is in doubt, they will refer. [22, 61] Again, greater emphasis needs to be placed on the detection of potentially malignant and premalignant lesions if a decrease in delay is sought.

Not only does referral involve the practitioner identifying and referring a patient for examination, there is a distinct need to communicate to the patient why they are being referred. A part of professional delay that is difficult to control for in studies is patient mediated professional delay, that is when patients do not attend a specialist appointment for a prolonged period of time following referral.[10] The need for a patient to promptly attend a specialist appointment should be communicated to the patient without causing undue distress. Rogers *et al.* found 1 in 6 patients were not satisfied with advice received upon their first medical consultation, however whether patients were dissatisfied with either advice given from a doctor or dentist was not represented and the reasons they weren't happy was also not explored.[42] The practitioner should be able gauge the patient's emotional and social well being and deliver medical information that the patient is able to comprehend.[36] Upon issuing a referral, practitioners will often tell the patient they have seen something suspicious and would like a second opinion.[6] Dentists worry about using language to avoid anxiety, tending to refrain from using words associated with malignancy and some believe this helps calm the patient.[6] Following questioning from the patient regarding possibility of oral cancer, dentists tend to say they do not think the lesion is malignant.[6] Although this may help decrease patient anxiety, there is also a need to ensure that the patient also sees the issue of obtaining a definitive diagnosis as urgent. Both medical and dental practitioners believe more training in detection and referral pathways are necessary.[37]

4.6 Delays between diagnosis and treatment

Once a diagnosis of oral cancer has been made, delay can occur in obtaining treatment for these patients. Not only does this delay cause stress to the patient, tumour size may increase during this time period.[74] Alarmingly, a study in Denmark showed the amount of delay increased from 1992 to 2002. This was attributed to a shortage of radiotherapy capacity.[75] They also observed that more imaging procedures were carried out, but could not prove a cause and effect relationship.[75] In one study factors such as ethnicity, primary site and insurance correlated with delay between diagnosis and treatment.[76] It has been suggested

that longer planning time is needed for complex cases, thus some delay in this instance appears warranted.[76]

5. Health system factors

The structure and organisation of a country's health system is a critically important yet poorly recognised factor influencing the early detection of oral cancer and pre-cancer. It can contribute to both patient and professional delay. Low socioeconomic status has been previously discussed in this chapter as a barrier to accessing health care for the symptoms of oral cancer. Financial barriers to health care depend on the funding model of the health system. If health care is funded by the government then theoretically this barrier is removed. However, real access to public health care also depends on the available resources. Inadequately resourced public health care results in waiting lists. This forces patients to seek care in the private sector, or to neglect health care. In addition, health systems that ensure culturally safe practice enhance access for groups at high risk, Indigenous and recent immigrant populations.[77] Whether the health system values and supports prevention and early detection will influence practitioner behaviour in performing a thorough screen including a risk assessment and providing support for patients in modifying their health behaviours. If the practitioner is reimbursed for these activities or in the case of the public sector, if this contributes to productivity targets, then these behaviours are likely to be valued by the patient and occur more frequently.

Health systems globally are stretched ever further dealing with the challenges of an ageing population and the increased burden of complex chronic diseases. Dental health systems are often prioritised lower than general health systems and so public funding for oral health care may suffer a significant shortfall. Oral cancer, similarly to other oral disease, is almost entirely preventable. If it can be detected early, the outcomes are substantially better. Putting aside the gains in human health and quality of life, from a purely cost perspective, it makes sense to invest in programs which focus on the prevention and early detection of all oral diseases, including oral cancer. The health care team paradigm is now well accepted as a necessity for providing optimal patient care. In a number of countries, including Australia and New Zealand, oral health therapists are tertiary trained practitioners who work in the dental team. They have expertise in recognition of oral abnormalities, risk assessment and health promotion.[78] Novel models of care, in which oral health therapists are used to screen, risk assess, provide support for health behaviour modification and refer for treatments outside their scope of practice, are currently being trialled. Continuing education programs, and the establishment of clear clinical guidelines and criteria for referral[79] are agreed to be necessary to support primary care clinicians in confidently and effectively performing oral cancer screening for their patients.

6. Diagnostic aids

The quest for reduction in professional delay of detection, and a desire to improve early detection of oral cancer has driven the development of diagnostic aids designed to improve visualisation of malignant and potentially malignant oral lesions. Methods for visualising and detecting PMOLs include conventional oral examination (COE), vital tissue staining, light based detection systems which rely on tissue reflectance (ViziLite, Microlux/DL), and

autofluorescence (VELscope, Identafi). Several key issues are considered when assessing a particular diagnostic aid. These include the effectiveness of the visualisation method in detecting oral cancer and precancer; whether or not the method can distinguish premalignant or malignant lesions from other benign conditions; and if an accepted "gold standard" comparison such as scalpel biopsy and histopathological assessment was used in assessing the efficacy of the diagnostic aid. Where possible, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are used to determine the effectiveness and accuracy of each aid. Sensitivity is the proportion of people who have the disease and test positive, while specificity refers to the proportion of people who do not have the disease and test negative. PPV is the proportion of people with positive test results who have the disease, whereas NPV is the proportion of people with negative results and do not have the disease.

6.1 Conventional oral examination

Conventional oral examination under normal incandescent or halogen light illumination is the standard method for screening for oral cancer.[5] It typically involves visual inspection of the oral cavity and palpation of the lymph nodes for clinical signs of abnormalities such as changes in colour, texture, ulceration, persistent swelling and enlarged lymph nodes.[1] Several studies have reported relatively high sensitivity and specificity values for COE. In a prospective study involving two oral cancer screening programs, over 2,300 people underwent a thorough oral examination by a dentist.[80] An oral medicine specialist then examined participants to give a definitive 'true' clinical diagnosis, thus providing a "soft" gold standard. The combined sensitivity and specificity of these two screening programs was 0.74 and 0.99 respectively,[80] which is consistent with sensitivity and specificity values of other screening programs.[81-83] The results from this study, along with six other prospective studies with calculated sensitivity and specificity, were included in a meta-analysis by Downer *et al*.[84] These studies reported a range of sensitivity and specificity values, from 0.60 to 0.97 and 0.74 to 0.99 respectively. When pooled together, the overall sensitivity for COE was 0.848 while the overall specificity was 0.965.[84] This indicates that COE has relatively few false negatives, and even less false positives. However, the ability of a clinician to screen for potentially malignant and malignant lesions will vary, depending on their knowledge and clinical judgement. Nonetheless, Downer *et al*.'s heterogeneity analysis of the eight studies found that dentists and specifically trained basic health workers can screen with similar degrees of accuracy.[84]

Despite the relatively high sensitivity and specificity, there is still some controversy about the use of COE as clinicians often cannot purely use this method to discriminate progressive from non-progressive lesions, and benign from malignant lesions.[85] For definitive diagnosis, an incisional biopsy with histopathological analysis is required.[1, 3] Furthermore, not all early lesions are easily seen under a dental operating light.[2, 5, 85, 86] In a pilot study by Thomson, 26 untreated patients with either a PMOL or unilateral OSCC had a biopsy of clinically normal-looking mucosa taken from the corresponding, contralateral anatomical site.[87] After histological assessment, 6 (23%) samples had reactive changes, 7 (27%) had some form of dysplasia (mild, moderate or severe), 1 (0.04%) had carcinoma in situ (CIS) and 1 (0.04%) had microinvasive squamous cell carcinoma.[87] Sites with a high proliferation rate such as the ventral tongue and floor of mouth, and were exposed to carcinogens, were also

found to be more susceptible to dysplastic changes.[87] It is therefore particularly important to identify high-risk patients so that an even higher level of suspicion is maintained when examining these patients, especially since a randomised controlled trial (RCT) reported a significant decrease in mortality in males who used alcohol or tobacco, or both, when they were screened for oral cancer.[88] However, a recent Cochrane review assessed this RCT and cautioned the interpretation of this statement, as the study had several methodological problems which may have introduced bias.[24] Furthermore, since this study was conducted in India where the prevalence of oral cancer is higher, results from this study may not be applicable to low-prevalence populations.[24] More RCTs are required as there currently is insufficient evidence to support oral cancer screening with COE in the general population. Nonetheless, it is clear that COE alone is not perfect. Therefore, the use of an adjunctive technique that has high specificity and sensitivity for highlighting PMOLs and OSCC should aid a clinician in detecting and diagnosing these lesions at an early stage, and consequently improve prognosis.[85]

6.2 Vital tissue staining

Tolonium chloride, more commonly known as toluidine blue (TB), is an acidophilic metachromatic dye of the thiazine group that preferentially stains nucleic acids and abnormal tissues.[5, 89] The increased nuclear density and the loss of intracellular adherence in dysplastic and malignant tissues allows TB dye to penetrate through the epithelium and be retained in these tissues, thereby staining these areas of abnormality blue.[89, 90] Although TB has primarily been marketed as an adjunct for detecting potentially malignant and malignant oral lesions not identified by COE, it has also been recommended for determining the risk of potentially malignant oral lesions progressing to cancer, monitoring suspicious lesions, determining the optimal biopsy site, assessing the extent and margins of potentially malignant and malignant oral lesions, and for assessing the outcome after treatment for dysplasia and cancer in follow-up appointments.[90, 91] Until recently, TB was commercially available as kits under the trade names 'OraScan' (Germiphene), 'OraScreen' (Stafford-Miller Ltd.) and 'OraTest' (Zila Pharmaceuticals). However, TB is now available as part of ViziLite Plus under the name, TBlue630 (Zila Tolonium Chloride) Oral Lesion Marking System, and may be used at the discretion of the clinician for demarcating any lesion that requires further study or biopsy.[92]

Whilst there is extensive literature on TB, many only provided background information, expert opinion and/or described a technique but did not provide additional data.[90] An early meta-analysis by Rosenberg *et al*. of 12 studies conducted between 1964 and 1984 reported 93.5 to 97.8% sensitivity and 73.3 to 92.9% specificity for the detection of oral cancers.[93] A later systematic review by Grey *et al*. of 14 studies conducted between 1970 to 1999, half of which were also included in Rosenberg *et al*.'s paper, reported sensitivity varying from 40 to 100% and specificity from 31 to 92%.[90] Another recent systematic review of adjuncts to oral examination assessed 15 studies from 1967 to 2005.[94] In this review, sensitivity and specificity of TB as a diagnostic adjunct ranged from 38 to 98% (median 85%) and 9 to 93% (median 67%) respectively. PPV varied from 33 to 93% (median 85%) and NPV from 22 to 92% (median 83%).[94] Although there are discrepancies in the sensitivity and specificity ranges due to the different inclusion and exclusion criteria of these reviews, the median values suggest that TB has high sensitivity but relatively lower specificity.

Findings from an observational study of 45 oral mucosal lesions by Allegra *et al*. are consistent with this idea.[95] Allegra *et al*. reported 96.2% sensitivity and 77.2% specificity for TB staining, with a PPV of 86.6% and a NPV of 93.3%. In comparison, sensitivity and specificity for clinical examination were 53% and 80% respectively, whereas the PPV was 84.2% and NPV was 46.1%. There was a statistically significant difference in both sensitivity and NPV between TB and clinical examination. Therefore, TB was better at identifying suspected lesions than COE, and had a very low probability of a positive histological result coming from a negatively stained lesion.[95] These results are consistent with previous studies.[96, 97] In contrast, a recently published paper of case series by Cancela-Rodriguez *et al*. reported higher specificity than sensitivity.[89] Whilst the sensitivity of 65.5% was lower than previous reports, the specificity of 73.3% was consistent with other studies. The PPV of 35.2% was also lower, which the authors attributed to the lower prevalence of dysplastic and malignant lesions in their study when compared with others, whereas the NPV of 90.6% was again consistent with other papers.[89]

On the whole, the relatively lower specificity values were a result of relatively high numbers of false positive findings. In several studies, TB stained normal variations of anatomy, and benign inflammatory and traumatic lesions due to their increased cell activity.[89, 96-100] To reduce the number of unnecessary biopsies and to exclude inflammatory and traumatic lesions, Mashberg suggested restaining any TB-stained lesion after 10 to 14 days.[98] Any lesion that still stained after this period should be evaluated for cancer by biopsy,[98] as OSCC, CIS and high-grade dysplasia retained TB fairly consistently.[5, 97, 101] Furthermore, a prospective longitudinal study by Zhang *et al*. reported that lesions – including benign lesions with high-risk clinical and molecular characteristics – which stained with TB had an increased risk of malignant transformation.[101] However, staining of all early-stage dysplasias does not always occur,[5] probably because these lesions do not have the molecular changes associated with OSCC progression.[102] Conversely, TB has been shown to stain lesions that were undetected by COE.[90, 103]

Current literature suggests that the use of TB by trained and experienced practitioners may be useful in high-risk patients in a specialist setting, as most TB studies have been conducted in specialist clinics on higher-risk patients or patients who already have a known lesion.[5, 94] With only one published community-based randomised controlled trial (RCT),[104] there is insufficient data to support the use of TB as an adjunct to COE in general practice on the general population. In this RCT, 7,975 participants were randomly allocated to either the experimental group (TB) or the control group (placebo dye), and were visually examined by experienced dentists who were trained by an oral pathologist to detect oral lesions. It was found that the use of TB did not significantly improve the detection rate of PMOLs; however, significantly more oral submucous fibrosis and slightly more leukoplakia were detected when TB was used as an adjunct than with visual screening alone. In addition, there was no significant difference between the two groups in reducing the incidence of oral cancer after five years. Further RCTs in the general population with longer follow-up periods are needed to confirm these results, particularly since the malignant transformation of PMOLs has a long natural history.[104]

Problems with experimental design and analysis of results are the main reasons contributing to the poor quality of many studies on TB. Care must be taken when interpreting and comparing results as methods and definitions are inconsistent. Common issues that need to

be considered include whether or not a non-pharmaceutical grade (laboratory) TB solution or a higher standard, pharmaceutical grade TB solution was used, the method of applying TB (rinse versus local swab), if a two rinse procedure was used instead of one rinse to rule out inflammatory lesions, and the definition of a positive stain. Staining intensity is a contentious issue, with some studies defining a positive result if there is an intense blue stain, while in other studies a positive result is if there is any blue staining.[5, 91] Further complicating this matter is the inclusion of equivocal results in some studies, and whether or not they should be considered as positive or negative in statistical analysis. Grey *et al*. showed that equivocal results can significantly affect statistical values in individual studies,[90] which may mean that accuracy results are underestimated.[94] Interpretation of TB stains can therefore be difficult and its use should be limited to trained and experienced clinicians, otherwise there may be more unnecessary biopsies taken and higher numbers of false positive and negative results.

6.3 Tissue reflectance (ViziLite, Microlux/DL)

There are several screening devices marketed as adjuncts to COE that enhance tissue reflectance to aid clinicians to detect PMOLs and OSCCs. These devices include ViziLite Plus (Zila Pharmaceuticals, Phoenix, Arizona, USA), Microlux/DL (AdDent, Danbury, CT, USA) and Orascoptic DK (Orascoptic, a Kerr Company, Middleton, WI, USA).[1, 2, 85, 105] ViziLite Plus utilises a disposable chemiluminescent light packet to provide diffuse blue-white light between 490 to 510 nm in wavelength.[92, 106] Chemiluminescence occurs when a chemical reaction produces light which can vary in intensity, lifetime and colour depending on the type of reaction.[107] In contrast, Microlux/DL and Orascoptic DK use a diffuse white light from a battery-powered light-emitting diode (LED).[108] Regardless of the type of light, these devices claim to enhance tissue reflectance of oral tissues after the mouth has been rinsed with 1% acetic acid for 60 seconds.[92, 108, 109] According to the manufacturers, a cytoplasmic dehydration agent such as acetic acid can alter the refractile properties of oral mucosal abnormalities with atypical non-keratinized squamous epithelium, as these cells have an increased nuclear:cytoplasmic ratio.[92, 108, 109] Consequently, dysplastic lesions become more visible as they appear white (hence termed an 'acetowhite lesion') against the light blue appearance of normal tissue.[85, 92, 105, 108-110]

Several studies have evaluated the efficacy of tissue reflectance as a technique for visualising and detecting oral mucosal lesions; however, the number of publications available is still quite limited. The majority of these are on ViziLite, with only one study on Microlux/DL and none on Orascoptic DK.[5] Although several studies have been published regarding the efficacy of ViziLite, there appears to be conflicting results. In a pilot study involving 150 patients, a variety of hard and soft oral lesions were examined using ViziLite.[110] All benign lesions without hyperkeratinisation, hyperparakeratinisation, chronic inflammatory infiltrate and/or an altered nuclear:cytoplasmic ratio did not appear acetowhite. However, all lesions with a clinical diagnosis of leukoedema and two out of fourteen frictional keratoses were ViziLite positive. In addition, three leukoplakic lesions appeared acetowhite. Two of these, including the one that was not detected by COE, had signs of cellular atypia, while the third was later diagnosed as a non-specific ulcer.[110] This finding is consistent with two other papers that reported positive results with a non-specific ulcer,[105] and four cases of traumatic ulcers.[111] These results suggest that ViziLite has fairly high

sensitivity but low specificity and PPV,[5] and this idea is supported by several studies.[105, 107, 112] In a study by Ram and Siar involving 40 patients with a PMOL, primary squamous cell carcinoma, or a history of either condition, sensitivity and specificity was 100% and 14.2% respectively.[107] In another study by Farah and McCullough involving 55 patients with an oral white mucosal lesion, sensitivity was again 100% while specificity was 0%.[105] Unlike Ram and Siar who reported an accuracy of 80.6%, Farah reported an accuracy of only 18.2%.[105, 107] This considerable difference in accuracy is most likely attributed to the different sample population.[105] A recent study by Awan *et al*. also reported high sensitivity and low specificity, with the values being 77.3% and 27.8% respectively.[112] The lower sensitivity has been attributed to the sample population, which included a wider range of oral lesions than the two previous studies.[112] In contrast, a recent study reported a sensitivity of 0% and specificity of 75.5%.[113] In this study by Mehrotra *et al.*, there were three dysplastic lesions and one cancerous lesion out of 102 patients examined with ViziLite – none of which had a positive ViziLite result. Consequently, the NPV was very high, at 94.8%, while PPV was 0%.[113] Although not specified by the authors, the dysplastic and cancerous lesions may have been red, which is reportedly less preferentially highlighted by chemiluminescence than lesions with a white component.[111, 112, 114] This may be due to the fact that erythroplakia has either atrophied epithelium or epithelium that has had no change in thickness, and that acetic acid does not enhance the refractile properties of erythroplakia.[111]

Clearly, the ability to differentiate between keratotic, inflammatory, potentially malignant and malignant lesions is poor with ViziLite.[105, 107, 111] Nevertheless, there are reports that ViziLite improves visualisation of lesions – particularly leukoplakias, although there are conflicting results. Epstein *et al*. found a significant improvement in the brightness, sharpness and texture of lesions using ViziLite,[114] while Kerr *et al*. noticed a significant improvement in only sharpness, a trend towards enhanced brightness, and no significant improvement in texture.[111] Two other studies also noticed improved brightness and sharpness of oral lesions with chemiluminescence.[112, 115] Visualisation of intraoral lesions was reportedly enhanced in Farah's paper, however this was not statistically significant.[105] In contrast, visualisation can be more difficult due to an increase in mucosal surface reflectivity as a result of stimulated salivary flow following an acetic acid rinse.[106, 111, 112] Most studies have also found at least one new lesion that was not seen by COE;[105, 106, 110, 111, 114] however, the general consensus is that ViziLite does not provide any additional benefit to COE.[105, 106, 113]

Although there have been several studies on ViziLite, the only published study assessing the efficacy of Microlux/DL as a diagnostic aid in visualising oral mucosal lesions is a prospective study by McIntosh *et al*.[85] In this study, 50 patients referred to an oral medicine specialist unit because of an oral mucosal white lesion were examined by an oral medicine specialist. Lesions were assessed clinically and were given a provisional diagnosis before undergoing incisional biopsy and histopathological analysis. With a gold standard diagnostic test to compare to, sensitivity, specificity, PPV and NPV could be accurately assessed. Results from this study found a sensitivity of 77.8%, a specificity of 70.7%, a PPV of 36.8% and a NPV of 93.5%. These results indicate that while Microlux/DL is fairly good for highlighting potentially malignant oral mucosal lesions and the presence of no disease, the ability to differentiate between benign and malignant lesions is poor. Furthermore, the

system did not find any new lesions, modify the provisional diagnosis, or change the biopsy site, although it did improve lesion visibility and border distinctness of the majority of lesions when compared to COE. Furthermore, the emitted light from Microlux/DL was found to be very similar to a standard LED headlight.[85] From these results alone, Microlux/DL does not appear to be a great benefit to COE, particularly since the sensitivity and specificity scores in this study are lower than Downer *et al.*'s calculated overall sensitivity and specificity for COE.[84, 108] A limitation of the study was that a specialist performed the examinations rather than a general dental practitioner, and more trials are required to validate these findings in a general population.[85] A significant finding however, was that examination of PMOLs with white light is more useful than standard incandescent or halogen light.

More research is needed to support the use of chemiluminescence and tissue reflectance as an adjunct to COE. The published papers on both ViziLite and Microlux/DL have flaws in their experimental design; the most common being the lack of a definitive diagnostic gold standard comparison (incisional biopsy and histopathology) for all lesions.[106, 107, 110, 111, 114] To compensate, several studies used results from brush cytology as their main diagnostic comparison,[106, 110, 114] but this does not provide a definitive diagnosis.[5] Other weaknesses in studies include small sample size,[85, 105, 107] recruiting patients from specialist clinics instead of from the general population,[85, 105, 107, 111] and the use of specialists instead of general dental practitioners.[85, 105, 111] As a consequence, results should be interpreted with caution as they cannot be generalised to general practitioners, nor to the general population where the prevalence of oral cancer and precancer is much lower.[115] In addition, there was a potential for conflicts in interest in two studies.[114, 115] Larger, well-designed clinical trials are required to determine the ability of these devices in improving the visualisation of potentially malignant lesions that cannot be identified by COE.[5]

6.4 Tissue autofluorescence imaging (VELscope, Identafi)

Another light-based adjunct to COE is a handheld device called a Visually Enhancing Lesion Scope (VELscope; LED Dental Inc., Burnaby, BC, Canada). Using the idea that cellular fluorophores are excited by high intensity light of particular wavelengths, this device utilizes blue light 400 to 460 nm in wavelength to cause tissue autofluorescence.[5] This technology is based on the fact that both the superficial epithelium and underlying stroma of developing premalignant lesions have changes in their optical properties.[116] Normal oral epithelium appears pale green when directly viewed through a narrow-band filter, as green-red fluorescence is excited from fluorophores in the oral tissues.[1, 2, 5, 117] In contrast, dysplastic cells or potentially early tumours appear dark green to black due to the cellular and structural changes which occur in neoplastic tissue.[1, 5, 117, 118] Cellular alterations such as decreased flavin adenine dinucleotide concentration and collagen matrix breakdown have been associated with loss of fluorescence visualisation (FV).[117, 118] Furthermore, decreased fluorescence as a result of increased absorption and scattering of light occurs when there are structural changes in both the epithelium and lamina propria such as hypertrophy, hyperchromatism, cellular/nuclear pleomorphism and increased microvascularity.[117, 118]

Being relatively new, the number of published literature about the efficacy of VELscope for visualising and detecting potentially malignant lesions is limited. While the general consensus is that VELscope has very high sensitivity, the specificity has ranged quite

considerably depending on the study. In three observational (cross-sectional) studies, the reported values for sensitivity ranged from 97% to 100% and for sensitivity, 80% to 100%.[117-119] In contrast, while Awan *et al*. had fairly high sensitivity, specificity was significantly lower.[112] The reported sensitivity for dysplasia and leukoplakia/erythroplakia was 84.1% and 87.1% respectively, while the specificity was 15.3% and 21.4% respectively.[112] Two recent studies have noted both low specificity and sensitivity with VELscope.[113, 120] A cross-sectional study by Mehrotra *et al*. found 50% sensitivity and 38.9% specificity after examining 156 patients seeking dental care with VELscope.[113] More recently, a prospective study by Farah *et al*. reported a sensitivity of 30%, a specificity of 63% and an accuracy of 55% when VELscope was used alone to examine 118 lesions from 112 patients.[120] The large discrepancy for specificity in these studies is most likely attributed to the sample population. Lane *et al*. and Poh *et al*. recruited patients with biopsy-confirmed oral dysplasia or SCC and Scheer *et al*. included patients with an increased risk of mucosal abnormalities.[117-119] In contrast, Mehrotra *et al*. enrolled patients with lesions deemed clinically innocuous according to COE,[113] while Farah *et al*. recruited patients with white or mixed white or red oral mucosal lesions,[120] and in the study conducted by Awan *et al*., the only inclusion criteria was the presence of white, red and mixed white and red oral lesions.[112] Only one study used VELscope in a private general dentistry practice.[121] In this retrospective observational study, 905 patients were examined with VELscope. The authors reported a 1.3% prevalence of mucosal abnormalities, with 83% of these lesions being potentially premalignant.[121] When compared with results from incisional biopsies, studies demonstrated that VELscope could reveal high-risk lesions such as severe dysplasia and CIS; however, milder forms of dysplasia were not always detected.[113, 117-119] Despite this, there are several published case studies of new lesions being uncovered with VELscope in patients with a history of epithelial dysplasia or CIS.[122, 123] Furthermore, Farah *et al*. reported that VELscope revealed five lesions not found during COE, enhanced visualisation of 34.74% of cases, changed the clinical provisional diagnosis of 22 lesions, and changed the biopsy site of four lesions.[120] Border distinctness and visibility of benign and dysplastic lesions, however, were not different.[120] VELscope may also play a role with reducing the risk of tumour recurrence as it can be used before the excision of lesions to delineate malignant and premalignant subclinical extensions.[118]

A high number of false positives with VELscope resulted in low specificity and PPV values, with reported PPV ranging from 6.4% to 54.5%, while NPV ranged from 97.5% to 100%.[113, 119, 120] Inflammatory and traumatic lesions such as oral lichen planus, granulation tissue, chronic inflammation, ulcerations and hyperkeratosis had loss of FV and were therefore false positive results.[119] These tissues displayed less autofluorescence as they also had increased submucosal blood flow, altered metabolic activity and structural changes.[113, 119] To discriminate inflammatory lesions from dysplastic lesions, soft pressure should be applied to reduce blood flow to the area.[120] Blanched inflammatory lesions will have normal autofluorescence whereas potentially malignant and malignant lesions remain unchanged.[113, 119-122] However, applied pressure to dysplastic and OSCC lesions can still cause blanching, even though these lesions had loss of fluorescence.[120] Interestingly, one study found a gain of autofluorescence in verrucous leukoplakias that had no dysplasia.[119] From this, the authors proposed that invasive carcinomas will also have a gain in autofluorescence and therefore, loss of fluorescence would not be an applicable indicator for malignancy in verrucous lesions.[119] Nonetheless, Balevi calculated, using Bayes' theorem

and the sensitivity and specificity values from existing literature, a PPV of 1.27% and a false positive rate of 98.63% if VELscope was used to routinely screen the total population for oral cancer.[124] The author concluded that as VELscope has such a high misdiagnosis rate in the general population, the use of VELscope should be limited to oral cancer specialist clinics where the prevalence of oral cancer is most likely greater than 10%.[124]

It is clear that there is currently an insufficient body of evidence to support the use of VELscope as an adjunct to COE for oral cancer screening in general practice. While VELscope does show promise, it cannot differentiate inflammatory and traumatic lesions from premalignant and malignant lesions. Therefore, use of the device requires skill and training in order to interpret results.[113, 119, 120] With low specificity, the clinician still needs to conduct a thorough examination and use their clinical judgement as well as the patient's history to determine the need for further investigation,[120] otherwise, there will be an increased risk of overtreatment and a higher number of unnecessary referrals.[112] Most published studies on VELscope have a small sample population that is not representative of the general population – namely, they were patients with a history of potentially malignant and malignant oral lesions.[117-120, 122, 123] In addition, a major limitation of VELscope is that the difference between loss of fluorescence and diminished fluorescence is subjective and depends on the experience of the user.[112, 119] When this is compounded with specialists who were not blinded,[117, 118] it is possible that results may have been overestimated. Consequently, the results from current literature cannot be applied to the general population and general practitioners. Until larger, blinded, randomized-controlled clinical trials can evaluate the performance of VELscope in populations where the prevalence for oral cancer is low, the use of this device should be restricted to specialist oral cancer clinics.

It is possible that the newest oral cancer screening system on the market, Identafi (previously marketed as Identafi 3000 ultra; DentalEZ Group, Malvern, PA, USA), may show more potential than its light-based screening predecessors. Identafi utilizes both optical autofluorescence and reflectance spectroscopy, in addition to traditional white light, to screen for PMOLs and OSCC.[86] According to the manufacturer, areas with biochemical and morphological changes in cells can be visually identified by exciting oral tissues using a combination of multi-spectral light.[86] Although highly concentrated white light may be considered slightly better for visualising oral lesions than incandescent operatory lights,[85] it cannot be used alone as it is still difficult to differentiate premalignant lesions with inflammation, oral lichen planus/lichenoid reactions and other benign conditions which clinically appear similar to precancer.[125] Consequently, the device also employs violet and green-amber light for detecting changes in fluorescence and reflectance respectively, thereby making it possible to locate areas of diseased tissue.[86]

Unlike VELscope which uses blue light, Identafi uses violet light to excite tissues and induce fluorescence.[86] As dysplastic and cancerous tissues have lower blue-green fluorescence intensity than normal tissues when they are excited by light with wavelengths between 330 to 470 nm,[116] abnormal tissues should appear dark brown or black when exposed to the 405 nm violet light emitted by Identafi.[86] A study by Roblyer *et al*. found that the optimal excitation wavelength of light for discriminating normal tissue from dysplasia and invasive cancer is 405 nm.[125] At this wavelength, the authors reported a sensitivity of 95.9% to 100% and a specificity of 91.4% to 96.2% for differentiating dysplasia and cancer from normal tissue.[125] Based on these results, it can be expected that Identafi may have similar values for

sensitivity and specificity. A recent case report illustrated how autofluorescence tissue imaging with Identafi aided in diagnosing a metastatic tumour that was clinically innocuous.[126] Furthermore, an unpublished study by Zuluaga *et al*. involving 120 patients from four clinical centres found that the violet light had 100% NPV and a PPV nearing 60% for differentiating between normal and dysplastic or malignant tissue in one cohort.[127] The other cohorts had similar findings, and the authors expect that the overall PPV will be improved in the entire cohort with the addition of green-amber light.[127]

Tissue reflectance can be enhanced with the addition of green-amber light (dominant 545 nm).[86, 127] Although the haemoglobin absorption is strongest at 420 nm,[128] this light can delineate the vasculature of lesions from surrounding normal tissues as its wavelength is close to one of the two primary bands of haemoglobin absorption (*Q*-band peak of 542 nm).[86, 128] Premalignant and malignant tissues will appear diffuse due to their disorganised growth of blood vessels.[86] Therefore, as abnormal signs of morphologic changes can be highlighted, the addition of this light is expected to reduce the rate of false positives.[86, 127] However, further research is required to determine the efficacy of a multispectral system like Identafi.

7. Conclusions

Morbidity and mortality rates for oral cancer can be improved if potentially malignant oral mucosal lesions are found before they reach an advanced stage. Investigation of socio demographic factors in relation to patient delay is an important area deserving of further attention. Themes have emerged through the use of qualitative studies regarding barriers and triggers to patient presentation. Drawing upon the triggers associated with help seeking behavior and creating awareness of the symptoms of oral cancer may allow patients to attribute their signs to something more serious. Educational interventions and self screening promotion aimed at the population have the potential to create awareness of oral cancer. Patients have stated that if they were more aware of oral cancer, they would have presented sooner regarding their signs and symptoms. As it has been shown that patients often tell a family member or friend about their symptoms, increased knowledge among the public may ensure that the patient is advised to seek help by their loved ones. Educational interventions should also be targeted at pharmacists, as their advice has the potential to decrease patient delay should a patient seek advice from a pharmacy.

Dentists should be performing opportunistic screening on patients at dental appointments; however this is not happening consistently. Lack of confidence signals the need for further training, which can be done at both the undergraduate level and following graduation in the form of continuing professional development. As patients will commonly present to their doctor regarding an oral lesion, continuing education courses should also be made available for doctors. Identification of risk factors and effective patient counseling has the potential to decrease the incidence of oral cancer and there is need for improvement in this area. Risk factor analysis and effective communication could be integrated into continuing education courses. Practitioners should be more involved in creating awareness of oral cancer and this may be as simple as making pamphlets available at their surgeries.

Problems exist with interpreting data from many studies performed in this area. Often studies are performed retrospectively, thus incorporating memory bias or relying on records

which may be incomplete. The low incidence of oral cancer renders sample sizes small, making it difficult to generalize the results. Continued investigation of the barriers and triggers to help seeking behavior and identification of factors involved in professional delay is required in order to inform effective interventions.

Although many new diagnostic aids are available to help clinicians detect oral mucosal lesions earlier, the current screening devices and methods are limited by their inability to detect and discriminate between benign and malignant lesions, and thus cannot be used alone as an alternative to COE – they must be used as an adjunct. As skill and training are required in order to interpret results, the use of these devices and methods should be limited to specialist centres and experienced and trained clinicians, if they are to be recommended for use at all. Currently, there is still insufficient evidence to support the use of vital tissue staining and technology based on tissue reflectance and autofluorescence, particularly since none have consistently shown that they are more effective than COE.

8. References

[1] McCullough MJ, Prasad G, Farah CS. Oral mucosal malignancy and potentially malignant lesions: an update on the epidemiology, risk factors, diagnosis and management. *Aust Dent J.* Jun 2010;55 Suppl 1:61-65.

[2] Rethman MP, Carpenter W, Cohen EE, et al. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. *J Am Dent Assoc.* 2010;141(5):509-520.

[3] Neville BW, Day TA. Oral cancer and precancerous lesions. *CA Cancer J Clin.* Jul-Aug 2002;52(4):195-215.

[4] Warnakulasuriya S. Causes of oral cancer--an appraisal of controversies. *Br Dent J.* Nov 28 2009;207(10):471-475.

[5] Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral Oncol.* Jan 2008;44(1):10-22.

[6] Brocklehurst PR, Baker SR, Speight PM. A qualitative study examining the experience of primary care dentists in the detection and management of potentially malignant lesions. 2. Mechanics of the referral and patient communication. *Br Dent J.* 2010;208(2):E4; discussion 74-75.

[7] Farah CS, McCullough MJ. Oral cancer awareness for the general practitioner: new approaches to patient care. *Aust Dent J.* 2008;53(1):2-10.

[8] Scott SE, Grunfeld EA, Main J, McGurk M. Patient delay in oral cancer: a qualitative study of patients' experiences. *Psychooncology.* 2006;15(6):474-485.

[9] van der Waal I, de Bree R, Brakenhoff R, Coebergh JW. Early diagnosis in primary oral cancer: is it possible? *Med Oral Patol Oral Cir Bucal.* 2011;1(16):e300-305.

[10] Peacock ZS, Pogrel MA, Schmidt BL. Exploring the reasons for delay in treatment of oral cancer. *J Am Dent Assoc.* 2008;139(10):1346-1352.

[11] McLeod NM, Saeed NR, Ali EA. Oral cancer: delays in referral and diagnosis persist. *Br Dent J.* 2005;198(11):681-684.

[12] Abdo EN, Garrocho Ade A, Barbosa AA, et al. Time elapsed between the first symptoms, diagnosis and treatment of oral cancer patients in Belo Horizonte, Brazil. *Med Oral Patol Oral Cir Bucal.* 2007;12(7):E469-473.

[13] Rogers SN. Quality of life perspectives in patients with oral cancer. *Oral Oncol.* 2010;46(6):445-447.
[14] LeHew CW, Epstein JB, Kaste LM, Choi YK. Assessing oral cancer early detection: clarifying dentists' practices. *J Public Health Dent.* 2010;70(2):93-100.
[15] Gao W, Guo CB. Factors related to delay in diagnosis of oral squamous cell carcinoma. *J Oral Maxillofac Surg.* 2009;67(5):1015-1020.
[16] Grant E, Silver K, Bauld L, Day R, Warnakulasuriya S. The experiences of young oral cancer patients in Scotland: symptom recognition and delays in seeking professional help. *Br Dent J.* 2010;208(10):465-471.
[17] Pitiphat W, Diehl SR, Laskaris G, Cartsos V, Douglass CW, Zavras AI. Factors associated with delay in the diagnosis of oral cancer. *J Dent Res.* 2002;81(3):192-197.
[18] Scott S, McGurk M, Grunfeld E. Patient delay for potentially malignant oral symptoms. *Eur J Oral Sci.* 2008;116(2):141-147.
[19] Scott SE, Grunfeld EA, Auyeung V, McGurk M. Barriers and triggers to seeking help for potentially malignant oral symptoms: implications for interventions. *J Public Health Dent.* 2009;69(1):34-40.
[20] Scott SE, Grunfeld EA, McGurk M. Patient's delay in oral cancer: A systematic review. *Community Dent Oral Epidemiol.* 2006;34(5):337-343.
[21] McGurk M, Scott SE. The reality of identifying early oral cancer in the general dental practice. *Br Dent J.* 2010;208(8):347-351.
[22] Brocklehurst PR, Baker SR, Speight PM. Factors which determine the referral of potentially malignant disorders by primary care dentists. *J Dent.* 2010;38(7):569-578.
[23] Wade J, Smith H, Hankins M, Llewellyn C. Conducting oral examinations for cancer in general practice: what are the barriers? *Fam Pract.* 2010;27(1):77-84.
[24] Brocklehurst P, Kujan O, Glenny AM, et al. Screening programmes for the early detection and prevention of oral cancer. *Cochrane Database Syst Rev.* 2010(11):CD004150.
[25] Speight PM, Palmer S, Moles DR, et al. The cost-effectiveness of screening for oral cancer in primary care. *Health Technol Assess.* Apr 2006;10(14):1-144, iii-iv.
[26] Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LM. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. *Int J Cancer.* Jun 15 2008;122(12):2811-2819.
[27] Fakhry C, Gillison ML. Clinical implications of human papillomavirus in head and neck cancers. *J Clin Oncol.* Jun 10 2006;24(17):2606-2611.
[28] Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst.* Mar 19 2008;100(6):407-420.
[29] Scott SE, Rizvi K, Grunfeld EA, McGurk M. Pilot study to estimate the accuracy of mouth self-examination in an at-risk group. *Head Neck.* Oct 2010;32(10):1393-1401.
[30] Elango KJ, Anandkrishnan N, Suresh A, Iyer SK, Ramaiyer SK, Kuriakose MA. Mouth self-examination to improve oral cancer awareness and early detection in a high-risk population. *Oral Oncol.* Jul 2011;47(7):620-624.
[31] Gomez I, Warnakulasuriya S, Varela-Centelles PI, et al. Is early diagnosis of oral cancer a feasible objective? Who is to blame for diagnostic delay? *Oral Dis.* 2010;16(4):333-342.

[32] Hertrampf K, Wenz HJ, Koller M, Wiltfang J. Public awareness about prevention and early detection of oral cancer: A population-based study in Northern Germany. *J Craniomaxillofac Surg*. May 16 2011;[Epub ahead of print].

[33] Elango KJ, Anandkrishnan N, Suresh A, Iyer SK, Ramaiyer SK, Kuriakose MA. Mouth self-examination to improve oral cancer awareness and early detection in a high-risk population. *Oral Oncol.* 2011;47(7):620-624.

[34] Humphris GM, Field EA. The immediate effect on knowledge, attitudes and intentions in primary care attenders of a patient information leaflet: a randomized control trial replication and extension. *Br Dent J.* 2003;194(12):683-688.

[35] Laronde DM, Bottorff JL, Hislop TG, et al. Voices from the community--experiences from the dental office: initiating oral cancer screening. *J Can Dent Assoc.* 2008;74(3):239-241.

[36] Newton JT. Reactions to cancer: communicating with patients, family and carers. *Oral Oncol.* 2010;46(6):442-444.

[37] Macpherson LM, McCann MF, Gibson J, Binnie VI, Stephen KW. The role of primary healthcare professionals in oral cancer prevention and detection. *Br Dent J.* 2003;195(5):277-281.

[38] Kao SY, Chu YW, Chen YW, Chang KW, Liu TY. Detection and screening of oral cancer and pre-cancerous lesions. *J Chin Med Assoc.* 2009;72(5):227-233.

[39] Rodgers J, Macpherson LM. General dental practitioners' perceptions of the West of Scotland Cancer Awareness Programme oral cancer campaign. *Br Dent J.* 2006;200(12):693-697.

[40] Scott SE, Weinman J, Grunfeld EA. Developing ways to encourage early detection and presentation of oral cancer: What do high-risk individuals think? *Psychol Health.* Jan 1 2011;[Epub ahead of print]:1-14.

[41] Kerdpon D, Sriplung H. Factors related to delay in diagnosis of oral squamous cell carcinoma in southern Thailand. *Oral Oncol.* 2001;37(2):127-131.

[42] Rogers SN, Vedpathak SV, Lowe D. Reasons for delayed presentation in oral and oropharyngeal cancer: the patients perspective. *Br J Oral Maxillofac Surg.* Jul 29 2010;[Epub ahead of print].

[43] Rogers SN, Lowe D, Catleugh M, Edwards D. An oral cancer awareness intervention in community pharmacy. *Br J Oral Maxillofac Surg.* 2010;48(7):498-502.

[44] Kato I, Neale AV. Does use of alternative medicine delay treatment of head and neck cancer? A surveillance, epidemiology, and end results (SEER) cancer registry study. *Head Neck.* 2008;30(4):446-454.

[45] Rogers SN, Pabla R, McSorley A, Lowe D, Brown JS, Vaughan ED. An assessment of deprivation as a factor in the delays in presentation, diagnosis and treatment in patients with oral and oropharyngeal squamous cell carcinoma. *Oral Oncol.* 2007;43(7):648-655.

[46] Watson JM, Logan HL, Tomar SL, Sandow P. Factors associated with early-stage diagnosis of oral and pharyngeal cancer. *Community Dent Oral Epidemiol.* 2009;37(4):333-341.

[47] Jovanovic A, Kostense PJ, Schulten EA, Snow GB, van der Waal I. Delay in diagnosis of oral squamous cell carcinoma; a report from The Netherlands. *Eur J Cancer B Oral Oncol.* 1992;28B(1):37-38.

[48] Wildt J, Bundgaard T, Bentzen SM. Delay in the diagnosis of oral squamous cell carcinoma. *Clin Otolaryngol Allied Sci*. 1995;20(1):21-25.

[49] Morelatto RA, Herrera MC, Fernandez EN, Corball AG, Lopez de Blanc SA. Diagnostic delay of oral squamous cell carcinoma in two diagnosis centers in Cordoba Argentina. *J Oral Pathol Med.* 2007;36(7):405-408.

[50] Hollows P, McAndrew PG, Perini MG. Delays in the referral and treatment of oral squamous cell carcinoma. *Br Dent J.* 2000;188(5):262-265.

[51] Brouha XDR, Tromp DM, Hordijk GJ, Winnubst JAM, de Leeuw JRJ. Oral and pharyngeal cancer: Analysis of patient delay at different tumor stages. *Head Neck-J Sci Spec.* 2005;27(11):939-945.

[52] Sargeran K, Murtomaa H, Safavi SM, Teronen O. Delayed diagnosis of oral cancer in Iran: challenge for prevention. *Oral Health Prev Dent.* 2009;7(1):69-76.

[53] Paleri V, Wight RG, Silver CE, et al. Comorbidity in head and neck cancer: a critical appraisal and recommendations for practice. *Oral Oncol.* 2010;46(10):712-719.

[54] Brouha X, Tromp D, Hordijk GJ, Winnubst J, De Leeuw R. Role of alcohol and smoking in diagnostic delay of head and neck cancer patients. *Acta Otolaryngol Orient.* 2005;125(5):552-556.

[55] Santos LC, Batista Ode M, Cangussu MC. Characterization of oral cancer diagnostic delay in the state of Alagoas. *Braz J Otorhinolaryngol.* 2010;76(4):416-422.

[56] Lopez-Jornet P, Camacho-Alonso F. New barriers in oral cancer. Patient accessibility to dental examination--A pilot study. *Oral Oncol.* 2006;42(10):1022-1025.

[57] Alho OP, Teppo H, Mantyselka P, Kantola S. Head and neck cancer in primary care: presenting symptoms and the effect of delayed diagnosis of cancer cases. *CMAJ.* 2006;174(6):779-784.

[58] Morse DE, Velez Vega CM, Psoter WJ, et al. Perspectives of San Juan healthcare practitioners on the detection deficit in oral premalignant and early cancers in Puerto Rico: a qualitative research study. *BMC Public Health.* 2011;11(1):391.

[59] Scott SE, McGurk M, Grunfeld EA. The process of symptom appraisal: cognitive and emotional responses to detecting potentially malignant oral symptoms. *J Psychosom Res.* 2007;62(6):621-630.

[60] Kujan O, Duxbury AJ, Glenny AM, Thakker NS, Sloan P. Opinions and attitudes of the UK's GDPs and specialists in oral surgery, oral medicine and surgical dentistry on oral cancer screening. *Oral Dis.* 2006;12(2):194-199.

[61] Brocklehurst PR, Baker SR, Speight PM. A qualitative study examining the experience of primary care dentists in the detection and management of potentially malignant lesions. 1. Factors influencing detection and the decision to refer. *Br Dent J.* 2010;208(2):E3; discussion 72-73.

[62] Scott SE, Grunfeld EA, McGurk M. The idiosyncratic relationship between diagnostic delay and stage of oral squamous cell carcinoma. *Oral Oncol.* 2005;41(4):396-403.

[63] Guggenheimer J, Verbin RS, Johnson JT, Horkowitz CA, Myers EN. Factors delaying the diagnosis of oral and oropharyngeal carcinomas. *Cancer.* 1989;64(4):932-935.

[64] Cruz GD, Ostroff JS, Kumar JV, Gajendra S. Preventing and detecting oral cancer. Oral health care providers' readiness to provide health behavior counseling and oral cancer examinations. *J Am Dent Assoc.* 2005;136(5):594-601.

[65] Mahalaha SA, Cheruvu VK, Smyth KA. Oral cancer screening: practices, knowledge, and opinions of dentists working in Ohio nursing homes. *Spec Care Dentist.* 2009;29(6):237-243.

[66] Klosa K, Wiltfang J, Wenz HJ, Koller M, Hertrampf K. Dentists' opinions and practices in oral cancer prevention and early detection in Northern Germany. *Eur J Cancer Prev.* 2011;20(4):313-319.

[67] Jaber L, Shaban S, Hariri D, Smith S. Perceptions of healthcare practitioners in Saudi Arabia regarding their training in oral cancer prevention, and early detection. *Int J Health Care Qual Assur.* 2011;24(1):8-18.

[68] Carter LM, Ogden GR. Oral cancer awareness of general medical and general dental practitioners. *Br Dent J.* 2007;203(5):E10; discussion 248-249.

[69] Afifah R, Schwarz E. Patient demand for smoking cessation advice in dentist offices after introduction of graphic health warnings in Australia. *Aust Dent J.* 2008;53(3):208-216.

[70] Amagasa T, Yamashiro M, Uzawa N. Oral premalignant lesions: from a clinical perspective. *Int J Clin Oncol.* 2011;16(1):5-14.

[71] Patton LL, Elter JR, Southerland JH, Strauss RP. Knowledge of oral cancer risk factors and diagnostic concepts among North Carolina dentists. Implications for diagnosis and referral. *J Am Dent Assoc.* 2005;136(5):602-610.

[72] Tromp DM, Brouha XD, Hordijk GJ, Winnubst JA, de Leeuw JR. Patient factors associated with delay in primary care among patients with head and neck carcinoma: a case-series analysis. *Fam Pract.* 2005;22(5):554-559.

[73] Dimitroulis G, Reade P, Wiesenfeld D. Referral patterns of patients with oral squamous cell carcinoma, Australia. *Eur J Cancer B Oral Oncol.* 1992;28B(1):23-27.

[74] Jensen AR, Nellemann HM, Overgaard J. Tumor progression in waiting time for radiotherapy in head and neck cancer. *Radiother Oncol.* 2007;84(1):5-10.

[75] Primdahl H, Nielsen AL, Larsen S, et al. Changes from 1992 to 2002 in the pretreatment delay for patients with squamous cell carcinoma of larynx or pharynx: a Danish nationwide survey from DAHANCA. *Acta Oncol.* 2006;45(2):156-161.

[76] Caudell JJ, Locher JL, Bonner JA. Diagnosis-to-treatment interval and control of locoregionally advanced head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2011;137(3):282-285.

[77] Anderson LM, Scrimshaw SC, Fullilove MT, Fielding JE, Normand J. Culturally competent healthcare systems. A systematic review. *Am J Prev Med.* Apr 2003;24(3 Suppl):68-79.

[78] Tsang A. *Oral Health Therapy Programs in Australia and New Zealand.* 1 ed: Robert T Watts; 2010.

[79] Brocklehurst PR, Baker SR, Speight PM. Oral cancer screening: what have we learnt and what is there still to achieve? *Future Oncol.* Feb 2010;6(2):299-304.

[80] Jullien JA, Downer MC, Zakrzewska JM, Speight PM. Evaluation of a screening test for the early detection of oral cancer and precancer. *Community Dent Health.* Mar 1995;12(1):3-7.

[81] Downer MC, Evans AW, Hughes Hallet CM, Jullien JA, Speight PM, Zakrzewska JM. Evaluation of screening for oral cancer and precancer in a company headquarters. *Community Dent Oral Epidemiol.* Apr 1995;23(2):84-88.

[82] Ikeda N, Downer MC, Ishii T, Fukano H, Nagao T, Inoue K. Annual screening for oral cancer and precancer by invitation to 60-year-old residents of a city in Japan. *Community Dent Health.* Sep 1995;12(3):133-137.

[83] Mathew B, Sankaranarayanan R, Sunilkumar KB, Kuruvila B, Pisani P, Nair MK. Reproducibility and validity of oral visual inspection by trained health workers in the detection of oral precancer and cancer. *Br J Cancer.* 1997;76(3):390-394.

[84] Downer MC, Moles DR, Palmer S, Speight PM. A systematic review of test performance in screening for oral cancer and precancer. *Oral Oncol.* Mar 2004;40(3):264-273.

[85] McIntosh L, McCullough MJ, Farah CS. The assessment of diffused light illumination and acetic acid rinse (Microlux/DL) in the visualisation of oral mucosal lesions. *Oral Oncol.* Dec 2009;45(12):e227-231.

[86] Identafi: How it works. 2010; http://www.identafi.net/identafi. Accessed 16 April, 2011.

[87] Thomson PJ. Field change and oral cancer: new evidence for widespread carcinogenesis? *Int J Oral Maxillofac Surg.* Jun 2002;31(3):262-266.

[88] Sankaranarayanan R, Ramadas K, Thomas G, et al. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. *Lancet.* Jun 4-10 2005;365(9475):1927-1933.

[89] Cancela-Rodriguez P, Cerero-Lapiedra R, Esparza-Gomez G, Llamas-Martinez S, Warnakulasuriya S. The use of toluidine blue in the detection of pre-malignant and malignant oral lesions. *J Oral Pathol Med.* Apr 2011;40(4):300-304.

[90] Gray M, Gold L, Burls A, Elley K. *The clinical effectiveness of toluidine blue dye as an adjunct to oral cancer screening in general dental practice*2000.

[91] Epstein JB, Guneri P. The adjunctive role of toluidine blue in detection of oral premalignant and malignant lesions. *Curr Opin Otolaryngol Head Neck Surg.* Apr 2009;17(2):79-87.

[92] ViziLite Plus. http://www.zila.com/assets/file/ViziliteBlueTBlue630_0507.pdf. Accessed 16 April, 2011.

[93] Rosenberg D, Cretin S. Use of meta-analysis to evaluate tolonium chloride in oral cancer screening. *Oral Surg Oral Med Oral Pathol.* May 1989;67(5):621-627.

[94] Patton LL, Epstein JB, Kerr AR. Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature. *J Am Dent Assoc.* Jul 2008;139(7):896-905; quiz 993-894.

[95] Allegra E, Lombardo N, Puzzo L, Garozzo A. The usefulness of toluidine staining as a diagnostic tool for precancerous and cancerous oropharyngeal and oral cavity lesions. *Acta Otorhinolaryngol Ital.* Aug 2009;29(4):187-190.

[96] Epstein JB, Feldman R, Dolor RJ, Porter SR. The utility of tolonium chloride rinse in the diagnosis of recurrent or second primary cancers in patients with prior upper aerodigestive tract cancer. *Head Neck.* Nov 2003;25(11):911-921.

[97] Epstein JB, Oakley C, Millner A, Emerton S, van der Meij E, Le N. The utility of toluidine blue application as a diagnostic aid in patients previously treated for upper oropharyngeal carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* May 1997;83(5):537-547.

[98] Mashberg A. Tolonium (toluidine blue) rinse--a screening method for recognition of squamous carcinoma. Continuing study of oral cancer IV. *JAMA.* Jun 19 1981;245(23):2408-2410.

[99] Onofre MA, Sposto MR, Navarro CM. Reliability of toluidine blue application in the detection of oral epithelial dysplasia and in situ and invasive squamous cell carcinomas. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* May 2001;91(5):535-540.

[100] Warnakulasuriya KA, Johnson NW. Sensitivity and specificity of OraScan (R) toluidine blue mouthrinse in the detection of oral cancer and precancer. *J Oral Pathol Med.* Mar 1996;25(3):97-103.

[101] Zhang L, Williams M, Poh CF, et al. Toluidine blue staining identifies high-risk primary oral premalignant lesions with poor outcome. *Cancer Res.* Sep 1 2005;65(17):8017-8021.

[102] Guo Z, Yamaguchi K, Sanchez-Cespedes M, Westra WH, Koch WM, Sidransky D. Allelic losses in OraTest-directed biopsies of patients with prior upper aerodigestive tract malignancy. *Clin Cancer Res.* Jul 2001;7(7):1963-1968.

[103] Mashberg A. Reevaluation of toluidine blue application as a diagnostic adjunct in the detection of asymptomatic oral squamous carcinoma: a continuing prospective study of oral cancer III. *Cancer.* Aug 15 1980;46(4):758-763.

[104] Su WW, Yen AM, Chiu SY, Chen TH. A community-based RCT for oral cancer screening with toluidine blue. *J Dent Res.* Sep 2010;89(9):933-937.

[105] Farah CS, McCullough MJ. A pilot case control study on the efficacy of acetic acid wash and chemiluminescent illumination (ViziLite) in the visualisation of oral mucosal white lesions. *Oral Oncol.* Sep 2007;43(8):820-824.

[106] Oh ES, Laskin DM. Efficacy of the ViziLite system in the identification of oral lesions. *J Oral Maxillofac Surg.* Mar 2007;65(3):424-426.

[107] Ram S, Siar CH. Chemiluminescence as a diagnostic aid in the detection of oral cancer and potentially malignant epithelial lesions. *Int J Oral Maxillofac Surg.* Jul 2005;34(5):521-527.

[108] Microlux/DL. 2007; http://www.addent.com/docs/instructions/microlux-dl_english.pdf. Accessed 16 April, 2011.

[109] Orascoptic DK User Manual. http://www.orascoptic.com/cms-filesystem-action/manuals/um_ordk_old.pdf. Accessed 16 April, 2011.

[110] Huber MA, Bsoul SA, Terezhalmy GT. Acetic acid wash and chemiluminescent illumination as an adjunct to conventional oral soft tissue examination for the detection of dysplasia: a pilot study. *Quintessence Int.* May 2004;35(5):378-384.

[111] Kerr AR, Sirois DA, Epstein JB. Clinical evaluation of chemiluminescent lighting: an adjunct for oral mucosal examinations. *J Clin Dent.* 2006;17(3):59-63.

[112] Awan KH, Morgan PR, Warnakulasuriya S. Evaluation of an autofluorescence based imaging system (VELscope) in the detection of oral potentially malignant disorders and benign keratoses. *Oral Oncol.* Apr 2011;47(4):274-277.

[113] Mehrotra R, Singh M, Thomas S, et al. A cross-sectional study evaluating chemiluminescence and autofluorescence in the detection of clinically innocuous precancerous and cancerous oral lesions. *J Am Dent Assoc.* Feb 2010;141(2):151-156.

[114] Epstein JB, Gorsky M, Lonky S, Silverman S, Jr., Epstein JD, Bride M. The efficacy of oral lumenoscopy (ViziLite) in visualizing oral mucosal lesions. *Spec Care Dentist.* Jul-Aug 2006;26(4):171-174.

[115] Epstein JB, Silverman S, Jr., Epstein JD, Lonky SA, Bride MA. Analysis of oral lesion biopsies identified and evaluated by visual examination, chemiluminescence and toluidine blue. *Oral Oncol.* Jun 2008;44(6):538-544.

[116] Schwarz RA, Gao W, Daye D, Williams MD, Richards-Kortum R, Gillenwater AM. Autofluorescence and diffuse reflectance spectroscopy of oral epithelial tissue using a depth-sensitive fiber-optic probe. *Appl Opt.* Feb 20 2008;47(6):825-834.

[117] Lane PM, Gilhuly T, Whitehead P, et al. Simple device for the direct visualization of oral-cavity tissue fluorescence. *J Biomed Opt.* Mar-Apr 2006;11(2):024006.

[118] Poh CF, Zhang L, Anderson DW, et al. Fluorescence visualization detection of field alterations in tumor margins of oral cancer patients. *Clin Cancer Res.* Nov 15 2006;12(22):6716-6722.

[119] Scheer M, Neugebauer J, Derman A, Fuss J, Drebber U, Zoeller JE. Autofluorescence imaging of potentially malignant mucosa lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* May 2011;111(5):568-577.

[120] Farah CS, McIntosh L, Georgiou A, McCullough MJ. The efficacy of tissue autofluorescence imaging (VELScope) in the visualization of oral mucosal lesions. *Head Neck* 2011.

[121] Huff K, Stark PC, Solomon LW. Sensitivity of direct tissue fluorescence visualization in screening for oral premalignant lesions in general practice. *Gen Dent.* Jan-Feb 2009;57(1):34-38.

[122] Kois JC, Truelove E. Detecting oral cancer: a new technique and case reports. *Dent Today.* Oct 2006;25(10):94, 96-97.

[123] Poh CF, Ng SP, Williams PM, et al. Direct fluorescence visualization of clinically occult high-risk oral premalignant disease using a simple hand-held device. *Head Neck.* Jan 2007;29(1):71-76.

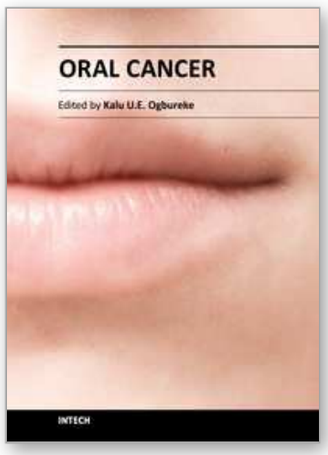
[124] Balevi B. Assessing the usefulness of three adjunctive diagnostic devices for oral cancer screening: a probabilistic approach. *Community Dent Oral Epidemiol.* Apr 2011;39(2):171-176.

[125] Roblyer D, Kurachi C, Stepanek V, et al. Objective detection and delineation of oral neoplasia using autofluorescence imaging. *Cancer Prev Res (Phila Pa).* May 2009;2(5):423-431.

[126] Vigneswaran N, Koh S, Gillenwater A. Incidental detection of an occult oral malignancy with autofluorescence imaging: a case report. *Head Neck Oncol.* 2009;1:37.

[127] Zuluaga AF, Vigneswaran N, Bradley RK, Gillenwater A, Nichols CM, Poh CF. Identafi®3000 ultra A multispectral tool for improved oral lesion evaluation. *Biomedical Optics.* Vol paper BSuD105. Miami, Florida: OSA Technical Digest (Optical Society of America); 2010.

[128] Rajaram N, Gopal A, Zhang X, Tunnell JW. Experimental validation of the effects of microvasculature pigment packaging on in vivo diffuse reflectance spectroscopy. *Lasers Surg Med.* Sep 2010;42(7):680-688.



Oral Cancer

Edited by Dr. Kalu U. E. Ogbureke

ISBN 978-953-51-0228-1
Hard cover, 388 pages
Publisher InTech
Published online 14, March, 2012
Published in print edition March, 2012

Oral cancer is a significant public health challenge globally. Although the oral cavity is easily accessible, early diagnosis remains slow compared to the enhanced detection of cancers of the breast, colon, prostate, and melanoma. As a result, the mortality rate from oral cancer for the past four decades has remained high at over 50% in spite of advances in treatment modalities. This contrasts with considerable decrease in mortality rates for cancers of the breast, colon, prostate, and melanoma during the same period. This book attempts to provide a reference-friendly update on the etiologic/risk factors, current clinical diagnostic tools, management philosophies, molecular biomarkers, and progression indicators of oral cancer.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

C. S. Farah, P. J. Ford, K. Allen, A. Vu and M. J. McCullough (2012). Oral Cancer and Potentially Cancerous Lesions - Early Detection and Diagnosis, Oral Cancer, Dr. Kalu U. E. Ogbureke (Ed.), ISBN: 978-953-51-0228-1, InTech, Available from: http://www.intechopen.com/books/oral-cancer/oral-cancer-and-potentially-cancerous-lesions-early-detection-and-diagnosis

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen